

# The role of fluid intake in the prevention of kidney stone disease: A systematic review over the last two decades

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## ABSTRACT

**Objective:** The incidence of kidney stone disease (KSD) is rising worldwide; hence, more focus must be directed toward its etiology and risk factors. Increasing fluid intake is recommended as the most ideal prevention; yet, there is inconsistent evidence surrounding optimum volumes and types of fluid that affect stone formation. This review aimed to analyze the published literature on fluid intake and types of fluid consumed and their impact on KSD prevention.

**Material and methods:** Papers were acquired from databases: MEDLINE, EMBASE, PubMed, CINAHL, and Cochrane Library. Included English language studies that involved adults consuming beverages along with a standardized diet in relation to KSD. Those failing to control dietary factors were excluded.

**Results:** After an initial search of 1099 papers, 9 (541 participants) were included in the final review. Six varieties of water and ten different types of juices were investigated. Higher fluid intake was associated with increased urine output and reduced stone formation. Water with high calcium content seemingly increased the rate of calcium oxalate (CaOx) stone formation. The relative supersaturation of CaOx in urine was decreased with grapefruit, apple, orange juices, and sodas, whereas cranberry juice increased it. Plum juice and the energy drink Gatorade had no effect on stone formation.

**Conclusion:** Fluids low in calcium seem to reduce the risk of KSD. Certain varieties of fluid, such as grapefruit, apple, and orange juices reduce urine CaOx saturation, with a subsequent reduction in stone formation. Findings from this review could contribute to primary prevention for those at risk of KSD.

**Keywords:** Drink; fluid; kidney stones; prevention; urolithiasis; water.

## Introduction

Kidney stone disease (KSD) is a recurrent condition affecting an increasing number of individuals worldwide.<sup>[1]</sup> Following an initial episode of stones, the risk of experiencing further episodes is 50% more likely within the first 5 years.<sup>[2]</sup> With this comes a significant financial burden for both health care services because of increased admissions and interventions, and the individuals themselves, because of time taken off work.<sup>[3]</sup>

Stone formation has been directly associated with a lack of fluid intake and is by far one of the most common causes of kidney stone formation. Low fluid intake leads to reduced diuresis, resulting in concentrated urine. This

may lead to supersaturation of minerals contributing to the formation of kidney stones.<sup>[2,4]</sup> Over 80% of worldwide kidney stones are made of calcium oxalate (CaOx)<sup>[2,5]</sup>, whereas uric acid stones make up 8%–10% of stones globally.<sup>[2]</sup>

The likelihood of developing kidney stones varies worldwide; a greater incidence is reported in North America (7%–13%), whereas the prevalence in Asia is approximately 1%–5%.<sup>[1]</sup> The current lifetime prevalence of experiencing kidney stones is approximately 14% in England,<sup>[6]</sup> and it is probable that 1 in 7 individuals are likely to receive care for KSD at some point.<sup>[7]</sup> These statistics emphasize the need for potential risk factors to be identified so that preventative measures can be introduced.

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Although multifactorial, countries associated with hot weather have been linked to KSD, with dehydration playing a major part.<sup>[1,7]</sup> This is important considering the current issues surrounding the rise in global temperatures. In addition to fluid intake, diet is a factor that can be controlled and has been mentioned as playing a key role in the formation of KSD in multiple papers.<sup>[8-11]</sup> Controlling the dietary intake of calcium and oxalate is important in stone formation, as well as ensuring a balanced diet is followed by increasing the intake of fruits and vegetables and cutting down on dairy and products with high fat content.<sup>[9,10]</sup>

Interventions for KSD vary from observation, to the use of medical expulsive therapy, ureteroscopy, shock wave lithotripsy, and percutaneous nephrolithotomy.<sup>[4]</sup> A study found that those undergoing invasive procedures were more likely to listen to and follow advice given regarding fluid intake, to prevent repeated interventions in the future.<sup>[12]</sup> Despite this, preventing stone formation in the first place is the cheapest form of protection, especially as etiological factors behind stone formation are not addressed by diagnostic procedures. Focusing on primary prevention would be of great benefit to health services especially in the long term, as it would save around £2000 per patient.<sup>[11]</sup>

The existing recommendation is to aim to drink enough to have a urine output of between 2 and 2.5 L per day.<sup>[13]</sup> Studies have found that caffeinated beverages are associated with a lower risk of KSD,<sup>[9]</sup> whereas sugary drinks increase the risk of stone formation because of high levels of fructose.<sup>[14]</sup> In addition, studies have also looked at the role of citric juices in nephrolithiasis, where an increase in the urinary elimination of citrate provides a protective effect by reducing the likelihood of stone formation.<sup>[15]</sup>

Although fluid intake has been proven to be an important factor in the prevention of KSD, there is limited evidence regarding the exact types and volumes of fluids, which contribute to the formation of kidney stones. As there is a need for further research into factors helping to prevent KSD, this paper aims to systematically review the current literature available on fluid intake in relation to KSD, to establish what is currently recommended. We also look at the relationship between various types and volumes of fluids with respect to KSD prevention.

#### Main Points:

- Certain varieties of fluid, such as grapefruit, apple, and orange juices reduce urine calcium oxalate saturation, with a subsequent reduction in stone formation.
- Higher fluid intake was associated with an increased urine output and reduced stone formation.
- Fluids low in calcium seem to reduce the risk of kidney stone disease.
- Findings from this review could contribute to primary prevention for those at risk of kidney stone disease.

## Material and methods

### Selection criteria

#### *Inclusion criteria:*

- Literature specific to KSD published between 2000 and 2019.
- Studies involving human adult participants (> 18 years).
- Studies comparing different types of fluids consumed alongside a standardized diet in relation to stone formation.
- Studies written in English.

#### *Exclusion criteria:*

- Animal studies.
- Laboratory studies.
- Review articles.
- Studies not controlling/failing to address dietary intake during study period.

### Search strategy and study selection

Five electronic databases were used to acquire the papers required for this review: Ovid MEDLINE (1946-2019), Embase Classic + Embase (1947-2019), CINAHL, PubMed, and Cochrane Library. The literature searching took place between October 2<sup>nd</sup> 2019 and November 20, 2019.

Search terms were split into kidney stone terms and fluid terms. Kidney stone terms included “kidney calculi,” “kidney stone disease,” “KSD,” “urolithiasis,” “nephrolithiasis,” “calculi,” “renal stone\*,” “ureteric stone\*,” “kidney stone\*,” “urinary stone\*,” “renal calculi,” “renal colic,” and “urinary calculi.” Fluid terms included “fluid\*,” “drinking water,” “hydrat\*,” “dehydrat\*,” “juice\*,” “tea,” “coffee,” “caffeine,” “alcohol,” “beverage\*,” “soda,” “fluid intake,” “hard water,” “soft water,” and “drink\*.” Boolean operators (AND, OR) were used and the term “prevent\*” was added after a combined search of the above had been done.

### Data collection and analysis

The “Preferred Reporting Items for Systematic Reviews and Meta-Analyses” guidelines were used to perform this review (Figure 1).<sup>[16]</sup> The references were imported into EndNote where duplicates were removed, and the remaining papers were screened in Microsoft Excel.

The initial screening process involved analysis of the titles and abstracts to see whether the studies fulfilled the inclusion criteria or were ineligible for further consideration. An independent investigator assessed the remaining articles on an Excel spreadsheet where relevant variables were extracted from each of the articles. The variables assessed were grouped, according to the study characteristics, participant characteristics, and highlighting key strengths and weaknesses.

## Results

The initial literature search across the five databases produced a total of 1099 results (293 from Ovid MEDLINE, 157 from Embase Classic + Embase, 23 from CINAHL, 425 from PubMed, and 201 from Cochrane Library). On removing 333 duplicates, 766 were screened by title and abstract, and after eligibility, 34 full texts were assessed. Of these 34, 25 were excluded because of having either no dietary information or due to the absence of a standardized diet (n=16), having no published results (ongoing clinical trials, n=3), not meeting the inclusion criteria (n=3). In addition, laboratory studies (n=2) and review paper (n=1) were also excluded. This left nine studies for inclusion in the systematic review (Figure 1).

### Study characteristics

Of the nine results, there were four cross-sectional studies, three cross-over studies, one case-control study, and one cohort study (Tables 1 and 2).

### Cross-sectional studies

Four cross-sectional studies<sup>[17-20]</sup> looked at a range of fluids: oligomineral water and bicarbonate-alkaline mineral water,<sup>[17]</sup> blackcurrant, cranberry, and plum,<sup>[18]</sup> and grapefruit, orange, and apple juices.<sup>[19]</sup> All four studies were conducted in European countries and all arms within each study were completed within 1 month. Urinary parameters were analyzed to look for biochemical changes between beverages via 24-h urine collections

and relative supersaturation values were calculated to assess the risk of future stone formation.

### Cross-over studies

Three cross-over studies<sup>[21-23]</sup> looked at further beverages: distilled water, orange juice and lemonade,<sup>[21]</sup> soda (caffeine-free Diet Coke and Fresca – type of orange soda)<sup>[22]</sup>, and a carbohydrate-electrolyte sports drink (Gatorade).<sup>[23]</sup> These were American studies and varied in terms of study completion length due to differing washout periods. Urinary parameters were also assessed in these studies to look for biochemical changes, along with relative supersaturation calculations to assess risk of stone formation in two of the studies.

### Case-control study

One American case-control study looked at the effect of cranberry juice against deionized water.<sup>[24]</sup> To again assess biochemical changes in the urine, 24-h urine collections were made, and the relative supersaturation ratio was measured.

### Cohort study

One Italian cohort study assessed the impact of Fiuggi water and tap water on stone formation in patients post lithotripsy.<sup>[25]</sup> Blood and 24-h urine samples were taken to assess the biochemical changes, as well as imaging techniques such as X-ray and abdominal echographic studies to look for stone recurrence every 6 months. This was the only study that had a clinical follow-up period (14–34 months) after the interventional period.

### Participant characteristics

#### Cross-sectional studies

All four cross-sectional studies<sup>[17-20]</sup> were conducted on healthy participants with no previous history of KSD. Sample sizes varied between all four studies (range: 9–48 participants)<sup>[17-20]</sup> with majority between 20 and 40 years of age, of which two studies focused solely on either males or females.<sup>[18,19]</sup>

#### Cross-over studies

Two of these studies were conducted on both healthy participants and recurrent stone forming patients,<sup>[21,23]</sup> whereas one only had healthy participants.<sup>[22]</sup> Sample sizes varied between all three studies (range: 6–24 participants).<sup>[21-23]</sup> Age range was a variable (Table 1) although the patients were relatively young.

#### Case-control study

The case-control study (n=24) involved both healthy participants and stone forming patients, split equally.<sup>[24]</sup> The mean age of healthy participants was 34.8±9.6 years and stone formers were 36.2±6.5 years<sup>[24]</sup> and all participants completed the study.

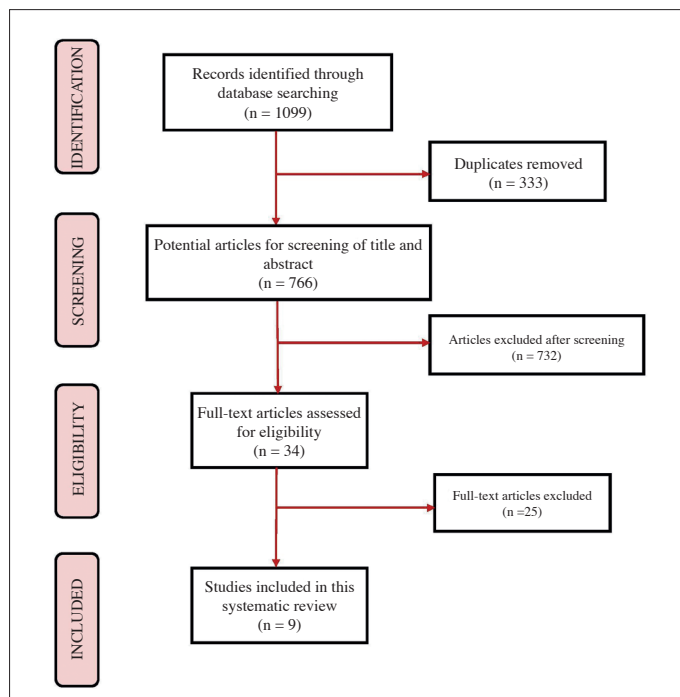


Figure 1. PRISMA flowchart

Table 1. Study and participant characteristics of articles reviewed

| Author                             | Journal                                | Country + Year of Study | Study Design + Duration  | Cohort  | Number of Participants  | Gender of Participants  | Mean Age±SD                                       | Type of Fluid                                       | Variables Assessed   |
|------------------------------------|--|-------------------------|--|---|---|---|---|---|--|
| Di Silverio et al. <sup>[25]</sup> | European Urology                       | Italy, 2000             | Cohort study, 2 weeks  | Patients treated with ESWL in past but clear of stones at time of study | • 384   | • Males (n=231)<br>• Females (n=153)  | • Males (28.3)<br>• Females (40.8)                | Finggi water and tap water                          | • Blood and 24-h urine samples for biochemical markers.<br>• X-ray and abdominal echographic studies (for stone recurrence).   |
| Coen et al. <sup>[17]</sup>        | Urologia Internationalis               | Italy, 2001             | Cross-sectional study, 2 weeks   | Healthy participants with no history of KSD                             | • 21 – divided into two groups:<br>- A (11: 6 males, 5 females)<br>- B (10: 5 males, 5 females) | • Males (n=11)<br>• Females (n=10)  | • Group A: 36±4<br>• Group B: 39.5±2.5            | Oligomineral water and bicarbonate-alkaline water   | • 24-h urine samples to measure biochemical markers.<br>• Risk of CaOx urinary supersaturation measured using Tiselius index.  |
| Kessler et al. <sup>[18]</sup>     | European Journal of Clinical Nutrition | Germany, 2002           | Cross-sectional study with four consecutive phases lasting 5 days each                 | Healthy participants with no history of KSD                             | • 12  | • Male  | • 29.3 (range: 18–38)                             | Plum juice, blackcurrant juice, and cranberry juice | • 24-h urine samples to measure biochemical markers.<br>• RSR for CaOx, uric acid, brushite and struvite calculated using EQUIL 2.   |
| Hönow et al. <sup>[19]</sup>       | British Journal of Nutrition           | Germany, 2003           | Cross-sectional study, 5 days per juice  | Healthy participants with no history of KSD                             | • 9   | • Female  | • 29 (range: 26–35)                               | Grapefruit juice, orange juice, and apple juice     | • 24-h urine samples to measure biochemical markers.<br>• Relative supersaturation for CaOx measured using EQUIL 2.<br>• BRI to determine crystallization risk of fresh urine samples. |
| Gettman et al. <sup>[24]</sup>     | The Journal of Urology                 | USA, 2005               | Case-control study with two 7-day phases with 3-week washout period between each phase | Healthy participants and patients with history of CaOx stones           | • 24 (12 healthy and 12 stone formers)  | • Healthy: males (n=6), females (n=6).<br>• Stone formers: males (n=6), females (n=6) | • Healthy: 34.8±9.6.<br>• Stone formers: 36.2±6.5 | Cranberry juice and deionized water                 | • Blood and 24-h urine samples to measure biochemical markers.<br>• RSR for CaOx, brushite, monosodium urate, and undissociated uric acid measured using EQUIL 2.                      |

Table 1. Study and participant characteristics of articles reviewed (Continued)

| Author                                   | Journal  | Country + Year of Study | Study Design + Duration  | Cohort  | Number of Participants  | Gender of Participants   | Mean Age $\pm$ SD  | Type of Fluid  | Variables Assessed   |
|--|--|-------------------------|--|---|---|--|--|--|--|
| Odvina et al. <sup>[21]</sup>            | Clinical Journal of the American Society of Nephrology | USA, 2006               | Cross-over study with three 7-day phases with 3-week washout period between each phase | Healthy participants and recurrent stone forming patients | <ul style="list-style-type: none"> <li>Start: 14 (10 healthy and 4 stone formers)</li> <li>End: 13 (9 healthy and 4 stone formers)</li> </ul>                         | <ul style="list-style-type: none"> <li>Healthy: males (n=5), females (n=4).</li> <li>Stone formers: males (n=3), females (n=1)</li> </ul>  | <ul style="list-style-type: none"> <li>Healthy: 44.7<math>\pm</math>9.6.</li> <li>Stone formers: 40.3<math>\pm</math>9.5</li> </ul>  | Orange juice, lemonade, and distilled water                  | <ul style="list-style-type: none"> <li>Blood and 24-hour urine sample collections to measure biochemical markers.</li> <li>RSR for CaOx, brushite and undissociated uric acid measured using EQUIL 2.</li> </ul> |
| Passman et al. <sup>[22]</sup>           | Journal of Endourology                                 | USA, 2009               | Cross-over study with three 5-day phases with 2-day washout period between each phase  | Healthy participants with no history of KSD               | <ul style="list-style-type: none"> <li>6</li> </ul>   | <ul style="list-style-type: none"> <li>Males (n=2)</li> <li>Females (n=4)</li> </ul>   | 28.8   | Le Bleu water, caffeine-free Diet Coke, and Fresca (citrate) | <ul style="list-style-type: none"> <li>24-h urine samples to measure biochemical markers.</li> <li>RSR for calcium phosphate and CaOx calculated using Tiselius index.</li> </ul>                                |
| Sweeney et al. <sup>[23]</sup>           | The Journal of Urology                                 | USA, 2009               | Cross-over study with three 7-day phases with 7-day washout period (4 weeks in total)  | Healthy participants and recurrent stone forming patients | <ul style="list-style-type: none"> <li>Start: 29 (14 healthy and 15 recurrent stone formers).</li> <li>End: 24 (12 healthy and 12 recurrent stone formers)</li> </ul> | <ul style="list-style-type: none"> <li>Healthy: males (n=5), females (n=7).</li> <li>Stone formers: males (n=2), females (n=10)</li> </ul> | <ul style="list-style-type: none"> <li>Healthy: 36.3<math>\pm</math>10.6.</li> <li>Stone formers: 38.8<math>\pm</math>7.7</li> </ul> | Gatorade and water   | <ul style="list-style-type: none"> <li>24-h urine sample and blood sample to measure biochemical markers.</li> </ul>   |
| de La Guéronnière et al. <sup>[20]</sup> | The Archives of Italian Urology and Andrology          | France, 2011            | Cross-sectional study with 3 weeks (two 1-week periods with 6-days control phase)      | Healthy participants with no history of KSD               | <ul style="list-style-type: none"> <li>48</li> </ul>  | <ul style="list-style-type: none"> <li>Males (n=27)</li> <li>Females (n=21)</li> </ul>   | <ul style="list-style-type: none"> <li>Males (29<math>\pm</math>4.6)</li> <li>Females (29.1<math>\pm</math>3.2)</li> </ul>           | Additional water intake or free water and fluid intake       | <ul style="list-style-type: none"> <li>24-h urine sample collection to measure biochemical markers.</li> <li>CRI measured using Tiselius index</li> </ul>  |

ESWL: extracorporeal shock wave lithotripsy; KSD: kidney stone disease; CaOx: calcium oxalate; RSR: relative supersaturation risk; BRI: BONN risk index; CRI: crystallization risk indices.

Table 2. Main findings of articles reviewed

| Author                             | Intervention   | Main Findings   | Strengths of Study  | Limitations of Study   | Drop-outs  | Useful for Future Applications?                         |
|------------------------------------|--|---|---|--|--|---|
| Di Silverio et al. <sup>[25]</sup> | <ul style="list-style-type: none"> <li>• Group A: 192 drank Fiuggi water.</li> <li>• Group B: 192 drank tap water.</li> <li>• 2L/day until follow-up (14–34 months)</li> </ul> | <ul style="list-style-type: none"> <li>• Stone recurrence in 17% of participants who had Fiuggi water, whereas 23% recurrence in group who had tap water with higher calcium content.</li> <li>• Risk of stone recurrence reduced with increased fluid intake.</li> <li>• Calciuria noted as a major risk factor in KSD.</li> </ul> | <ul style="list-style-type: none"> <li>• Large sample size using patients with stone recurrence problems – allows us to see the direct clinical effects without having to make assumptions.</li> <li>• Long follow-up period to properly monitor patients after intervention.</li> <li>• Urinary parameters were assessed as a way of seeing the immediate impact of fluids.</li> </ul>                                     | <ul style="list-style-type: none"> <li>• Length of follow-up was inconsistent between every patient (mean values given).</li> </ul>  | <ul style="list-style-type: none"> <li>• No</li> </ul> | <ul style="list-style-type: none"> <li>• Yes</li> </ul> |
| Coen et al. <sup>[17]</sup>        | <ul style="list-style-type: none"> <li>• Group A: oligomineral water.</li> <li>• Group B: bicarbonate-alkaline water.</li> <li>• 2 L/day for 2 weeks</li> </ul>                | <ul style="list-style-type: none"> <li>• Significant increase seen in urinary calcium excretion with bicarbonate-alkaline high calcium mineral water.</li> <li>• Higher CaOx supersaturation risk with bicarbonate-alkaline high calcium mineral water.</li> <li>• Increased urine output seen in both groups.</li> </ul>           | <ul style="list-style-type: none"> <li>• Sample size: Small but over ten in each group.</li> <li>• Results of significance can be applied to patients with recurring stone events.</li> <li>• Findings are supportive of the general recommendation of increasing fluid intake to reduce risk of stone formation.</li> <li>• Urinary parameters were assessed as a way of seeing the immediate impact of fluids.</li> </ul> | <ul style="list-style-type: none"> <li>• Did not compare effects of waters on a group of participants with a clinical diagnosis of KSD.</li> <li>• Length of study could have been longer to make more meaningful deductions and applications from the results.</li> <li>• Lack of clinical follow-up as focus was on looking at changes in urinary parameters.</li> </ul>   | <ul style="list-style-type: none"> <li>• No</li> </ul> | <ul style="list-style-type: none"> <li>• Yes</li> </ul> |
| Kessler et al. <sup>[18]</sup>     | <ul style="list-style-type: none"> <li>• Consuming one of three drinks for 4 days</li> <li>• Fifth day: Loading/control with mineral water</li> </ul>                          | <ul style="list-style-type: none"> <li>• Blackcurrant juice alkalinized urine, whereas cranberry juice had an acidifying effect.</li> <li>• Increased citric acid excretion with blackcurrant juice, decreased with cranberry juice.</li> <li>• No changes with plum juice.</li> </ul>  | <ul style="list-style-type: none"> <li>• Standardization of investigated results confirmed by results of urinary volume being almost the same.</li> <li>• Significance of results suggests potential ability to be clinically applicable recommendations for future practice.</li> <li>• Urinary parameters were assessed as a way of seeing the immediate impact of fluids.</li> </ul>                                     | <ul style="list-style-type: none"> <li>• No females in study, small sample, conducted on healthy individuals only.</li> <li>• One single day for control per fluid – potentially not an ideal way of implementing a control.</li> <li>• No record of volumes consumed.</li> <li>• Short control period.</li> <li>• Whole study could have been longer to make more meaningful deductions and applications from the results.</li> <li>• Lack of clinical follow-up as focus was on looking at changes in urinary parameters.</li> </ul> | <ul style="list-style-type: none"> <li>• No</li> </ul> | <ul style="list-style-type: none"> <li>• Yes</li> </ul> |

Table 2. Main findings of articles reviewed (Continued)

| Author                         | Intervention   | Main Findings   | Strengths of Study   | Limitations of Study   | Drop-outs   | Useful for Future Applications?                       |
|--------------------------------|--|---|--|--|---|---|
| Hönow et al. <sup>[19]</sup>   | <ul style="list-style-type: none"> <li>Fluid intake of 2.75 L (made of 2.25 L neutral mineral water, 0.4 L coffee, 0.1 L milk).</li> <li>Loading days: 0.5 L on day 4, 1.0 L on day 5 replaced by juice tested.</li> </ul> | <ul style="list-style-type: none"> <li>RSR for CaOx stones was reduced with all three juices.</li> <li>Statistically significant increase seen in citric acid excretion with all juices – provides protective effects.</li> <li>Concludes that grapefruit juice has no influence on stone formation risk</li> </ul> | <ul style="list-style-type: none"> <li>24-h urine volumes did not differ days 3–5=represents standardization.</li> <li>Findings are in line with previous studies, which confirms an emerging trend.</li> <li>Urinary parameters were assessed as a way of seeing the immediate impact of fluids.</li> </ul>   | <ul style="list-style-type: none"> <li>No males in study.</li> <li>Sample size small.</li> <li>Did not involve stone forming patients.</li> <li>Length of study could have been longer to make more meaningful deductions and applications from the results.</li> <li>Lack of clinical follow-up as focus was on looking at changes in urinary parameters.</li> </ul>  | <ul style="list-style-type: none"> <li>No</li> </ul>      | <ul style="list-style-type: none"> <li>Yes</li> </ul> |
| Gettman et al. <sup>[24]</sup> | <ul style="list-style-type: none"> <li>Phase 1: 1 L cranberry juice daily.</li> <li>Phase 2: 1 L deionized water</li> </ul>  | <ul style="list-style-type: none"> <li>Cranberry juice found to significantly increase calcium and oxalate levels.</li> <li>Cranberry juice lowered the urinary pH.</li> </ul>  | <ul style="list-style-type: none"> <li>Equal distribution of participants, gender spread, and healthy + stone formers (good matching).</li> <li>Study design well planned out and structured.</li> <li>A 3-week washout period provides a long time for the body to cleanse out the juice and allows for more accurate assumptions to be made from the study.</li> <li>Urinary parameters were assessed as a way of seeing the immediate impact of fluids.</li> </ul>  | <ul style="list-style-type: none"> <li>Small sample.</li> <li>Length of study could have been longer to make more meaningful deductions and applications from the results.</li> <li>Lack of clinical follow-up as focus was on looking at changes in urinary parameters.</li> </ul>  | <ul style="list-style-type: none"> <li>No</li> </ul>      | <ul style="list-style-type: none"> <li>Yes</li> </ul> |
| Odvina et al. <sup>[21]</sup>  | <ul style="list-style-type: none"> <li>Consumed either 400 mL orange juice, lemonade, or distilled water three times a day for 1 week with 3-week washout period</li> </ul>  | <ul style="list-style-type: none"> <li>RSR for CaOx stones was lower with orange juice than lemonade.</li> <li>Urinary citrate excretion was greater with orange juice.</li> </ul>  | <ul style="list-style-type: none"> <li>Intervention was clearly defined, and study was focused on the impact of the juices on the prevention of lithiasis.</li> <li>Potential confounding factors were eliminated (by ensuring medications were stopped 2 weeks before the start of the trial until the trial was completed, fixed ready-made diets provided for participants when in outpatient setting and having a fixed fluid intake).</li> <li>Urinary parameters were assessed as a way of seeing the immediate impact of fluids.</li> </ul> | <ul style="list-style-type: none"> <li>Carbohydrate content of orange and lemonade needs to be taken into consideration.</li> <li>Small sample, not an even split between healthy and stone forming patients.</li> <li>Length of study could have been longer to make more meaningful deductions and applications from the results.</li> <li>Lack of clinical follow-up as focus was on looking at changes in urinary parameters.</li> </ul> | <ul style="list-style-type: none"> <li>Yes - 1</li> </ul> | <ul style="list-style-type: none"> <li>Yes</li> </ul> |

**Table 2. Main findings of articles reviewed (Continued)**

| Author                                   | Intervention   | Main Findings  | Strengths of Study   | Limitations of Study   | Drop-outs   | Useful for Future Applications?                       |
|--|--|--|--|--|---|---|
| Passman et al. <sup>[22]</sup>           | <ul style="list-style-type: none"> <li>Consumed caffeine free-Diet Coke, Fresca, or Le Bleu bottled water over 5 days with 2-day washout period between types of fluid.</li> </ul> | <ul style="list-style-type: none"> <li>When on a controlled diet, decreased relative RSR for CaOx stones was seen with the sodas.</li> <li>However, sodas did not provide an increased benefit in comparison with bottled water.</li> </ul>                              | <ul style="list-style-type: none"> <li>Highlighted the importance of diet in relation to supersaturation risk.</li> <li>By controlling the diet in this study, the results differed from similar studies conducted in the past.</li> <li>Urinary parameters were assessed as a way of seeing the immediate impact of fluids.</li> </ul>  | <ul style="list-style-type: none"> <li>Very small sample size, possibly too small to note any major findings.</li> <li>Length of study could have been longer to make more meaningful deductions and applications from the results.</li> <li>Lack of clinical follow-up as focus was on looking at changes in urinary parameters.</li> <li>Study did not involve patients with KSD.</li> </ul> | <ul style="list-style-type: none"> <li>No</li> </ul>      | <ul style="list-style-type: none"> <li>Yes</li> </ul> |
| Sweeney et al. <sup>[23]</sup>           | <ul style="list-style-type: none"> <li>Phase 1: controlled diet.</li> <li>Phase 2: 2 L Gatorade/day.</li> <li>7-day washout period then phase 3: 2 L water/day.</li> </ul>         | <ul style="list-style-type: none"> <li>Urinary sodium and chloride levels were raised following consumption of Gatorade, but only slightly and not beyond normal ranges.</li> <li>No clinically relevant results were seen following consumption of Gatorade.</li> </ul> | <ul style="list-style-type: none"> <li>Studied effects on both healthy participants and stone forming patients.</li> <li>Participants got to meet with the dietician who put them on the standardized diet and then participants were reviewed throughout study – having this direct involvement and being able to tailor the diet/address concerns increases the validity of the study findings as compliance rates toward maintaining the constant diet were likely to be greater.</li> <li>Urinary parameters were assessed as a way of seeing the immediate impact of fluids.</li> </ul> | <ul style="list-style-type: none"> <li>Small sample.</li> <li>Length of study could have been longer to make more meaningful deductions and applications from the results.</li> <li>Lack of clinical follow-up as focus was on looking at changes in urinary parameters.</li> </ul>  | <ul style="list-style-type: none"> <li>Yes - 5</li> </ul> | <ul style="list-style-type: none"> <li>No</li> </ul>  |
| de La Guéronnière et al. <sup>[20]</sup> | <ul style="list-style-type: none"> <li>Assigned to treatment group (2 L/day additional water intake) or control group (usual fluid intake).</li> </ul>                             | <ul style="list-style-type: none"> <li>Crystallization index reduced in treated group, indicative of a protective effect of increasing fluid intake against stone formation.</li> </ul>  | <ul style="list-style-type: none"> <li>Good sample size.</li> <li>Focused on the volume of water.</li> <li>Standardized metabolic diets at set intervals during the study.</li> <li>Urinary parameters were assessed as a way of seeing the immediate impact of fluids.</li> </ul>   | <ul style="list-style-type: none"> <li>Study lacked evidence of effects on stone forming patients (was part of the study exclusion criteria).</li> </ul>   | <ul style="list-style-type: none"> <li>No</li> </ul>      | <ul style="list-style-type: none"> <li>Yes</li> </ul> |

ESWL: extracorporeal shock wave lithotripsy; KSD: kidney stone disease; RSR: relative supersaturation risk

### Cohort study

The cohort study involved 384 patients who had been treated with lithotripsy in the past.<sup>[25]</sup> There were 231 males (mean age of 28.3 years) and 153 females (mean age of 40.8 years).<sup>[25]</sup>

### Main findings of studies

In total, six varieties of water (oligomineral water and bicarbonate-alkaline high-calcium mineral water,<sup>[17]</sup> distilled water,<sup>[21]</sup> de-ionized water,<sup>[24]</sup> and Fiuggi and tap water<sup>[25]</sup>) and ten different types of beverages (blackcurrant juice,<sup>[18]</sup> cranberry juice,<sup>[18, 24]</sup>

plum juice,<sup>[18]</sup> grapefruit juice,<sup>[19]</sup> lemonade,<sup>[21]</sup> orange juice,<sup>[19, 21]</sup> apple juice,<sup>[19]</sup> caffeine-free diet Coke,<sup>[22]</sup> Fresca,<sup>[22]</sup> and Gatorade<sup>[23]</sup>) were looked at.

Di Silverio et al.<sup>[25]</sup> found that there was a 6% higher recurrence of nephrolithiasis in participants who consumed tap water with high calcium content than those who consumed Fiuggi water. Coen et al.<sup>[17]</sup> saw a significant increase in urinary calcium excretion following consumption of bicarbonate-alkaline calcium-rich mineral water, along with a higher relative supersaturation for CaOx stones. De La Guéronnière et al.<sup>[20]</sup> found that increasing fluid intake has a protective effect by reducing the crystallization index within urine, a finding that was also supported by Di Silverio et al.<sup>[25]</sup> (Table 2).

Kessler et al.<sup>[18]</sup> found that blackcurrant juice alkalinized urine, which could prevent uric acid stones, and increased citric acid excretion, whereas cranberry juice acidified urine and decreased citric acid excretion. No obvious changes were seen on urinary parameters following consumption of plum juice. The results of case-control study analyzing cranberry juice was in agreement with the finding that it acidifies urine.<sup>[24]</sup> However, it was also found to significantly increase calcium and oxalate levels. Relative supersaturation risk (RSR) for CaOx stones was reduced following an intake of grapefruit, orange, and apple juices, and an increase in citric acid excretion was seen with all three juices.<sup>[19]</sup> Odvina et al.<sup>[21]</sup> found a similar result for orange juice in their study.

When dietary factors were controlled, a lower RSR for CaOx stones was seen following consumption of caffeine-free diet Coke and Fresca,<sup>[22]</sup> highlighting the importance of diet in relation to supersaturation risk. However, this change was not noted as an increased benefit in comparison with bottled water.<sup>[22]</sup> A similar conclusion regarding actual benefit was made following the consumption of Gatorade, in relation to its lack of clinical relevance.<sup>[23]</sup>

## Discussion

This systematic review aimed to establish whether various types and volumes of fluids have a protective effect on the formation of kidney stones when consuming standardized diet in relation to stone formation.

### Urine output

This study provided findings from research conducted on six types of water and ten different types of juices in relation to KSD. A finding that was consistent among multiple studies was the fact that an increased urine output was seen with higher fluid intakes.<sup>[17-20,22]</sup> In three studies,<sup>[18,19,22]</sup> this was illustrated by the fact that having a controlled volume of fluid intake (often greater

than an individual's usual intake) during the intervention periods resulted in similar volumes of urine production among participants. These findings not only provided standardized urine volumes for analysis, but also support the noted correlation between increased fluid intake and increased urine output. Findings from a 5-year randomized prospective study confirmed the link back in 1996, and most recent studies continue to refer back to this study, as it is the only randomized trial with a long follow-up to have been conducted in relation to fluid intake and KSD.<sup>[26]</sup>

A review article noted that a urine output of less than 900 mL per day puts a healthy individual at a greater risk of developing stones, whereas the threshold for recurrent stone formers lies at around 1.6 L per day.<sup>[11]</sup> One study found that an increased water intake of 1.3 L in addition to normal fluid intake should be recommended.<sup>[20]</sup> However, it is important to note that patients with previous episodes of stone formation were excluded from the study, meaning that this value may need to be higher in those with a diagnosis of KSD.

All studies in this review had 24-h urine collections taken from the participants, allowing for biochemical changes to be seen within individual urinary parameters. An advantage of this is that the findings closely resemble kidney stone pathophysiology, meaning useful deductions can be made from observed changes, which is quicker than clinically following up patients.<sup>[27]</sup> Immediate conclusions can be drawn using 24-h urine collections; however, a clinical follow-up is preferred for predicting long-term KSD risk.

### Urinary pH

Urinary pH affects the probability of stone formation. Two studies found that cranberry juice decreased urinary pH, making urine more acidic.<sup>[18,24]</sup> The beverages identified in five studies (orange juice, Gatorade, bicarbonate-alkaline high-calcium mineral water, blackcurrant, apple juice, and grapefruit juice) were found to increase urinary pH, thus, making urine more alkaline.<sup>[17-19,21,23]</sup> Plum juice had no impact on urinary pH.<sup>[18]</sup> Acidic urine is thought to give rise to CaOx and uric acid stones, whereas alkaline urine gives rise to calcium phosphate, struvite, and brushite stones.<sup>[2]</sup> Therefore, it is important to have a balance with urinary pH by eating food and drinking beverages that favor a neutral to slightly acidic pH, but not so much that it goes toward one of the two extremes on the pH scale.

The findings from this study suggesting that orange juice makes urine more alkaline have been supported by previous literature.<sup>[1,14]</sup> However, these findings have been contradicted by Curhan et al.<sup>[28]</sup> reporting a small acidic effect with apple juice. It is important to note that although the study by Curhan et al.<sup>[28]</sup> involved 45,289 participants, all of these patients were male. This 1996 study<sup>[28]</sup> was followed up with another cohort study in

1998<sup>[29]</sup> involving 81,093 participants, all of which were female, and no significant difference was seen between apple juice consumption and risk of stone formation. The study on apple juice analyzed in this systematic review involved a lot fewer female participants.<sup>[19]</sup> This suggests that gender differences may affect the susceptibility to stone formation.<sup>[8]</sup>

Despite the statistically nonsignificant finding, Hönow et al.<sup>[19]</sup> reported that grapefruit juice was seen to make urine slightly alkaline, but this did not contribute toward the risk of stone formation with grapefruit juice. This is contradicted by the 1996 and 1998 study by Curhan et al.<sup>[28,29]</sup> and Taylor and Curhan<sup>[9]</sup> as they discussed how grapefruit juice tends to increase the risk of stone formation, though the reason behind this is unclear.

Although Gatorade was seen to increase urinary pH<sup>[23]</sup> and potentially be useful in the prevention of CaOx and uric stones, such results were not seen in a study conducted by Goodman et al.<sup>[30]</sup> and suggested that sports drinks should not be used to prevent stone formation owing to the amount of carbohydrate, calories, and fructose. Although the prevention of uric acid stones using Gatorade may be seen as favorable, most individuals with uric acid stones also suffer from diabetes, which may exacerbate sugar levels if given Gatorade.<sup>[30]</sup>

### Relative supersaturation risk

RSR is a calculation made using software to determine the risk of potential stone formation via the analysis of individual urinary factors that may promote or inhibit stone formation.<sup>[2]</sup> RSR calculations are often made in relation to the type of stones found. One study in this review found a decreased RSR for CaOx stones with orange, apple, and grapefruit juices, although the only statistically significant finding was seen for 500 mL of grapefruit juice in this particular study ( $p < 0.05$ ).<sup>[19]</sup> In the study comparing orange juice with lemonade, a decreased RSR for CaOx stones was seen with orange juice in comparison with distilled water and lemonade.<sup>[21]</sup> However, in the same study, the RSR for brushite stones was increased with intake of orange juice in comparison with distilled water and lemonade.<sup>[21]</sup> A decreased RSR for CaOx stones was also seen with caffeine-free diet coke, Fresca, and bottled water in comparison with a group consuming these drinks while on an uncontrolled diet.<sup>[22]</sup> However, a significant increase in the RSR for CaOx stones was seen with cranberry juice in one of the two studies that looked at cranberry juice.<sup>[24]</sup> Nevertheless, both studies confirmed that a decreased RSR for brushite stones was seen,<sup>[18,24]</sup> likely due to the fact that cranberry juice acidifies urine and, therefore, has a protective effect on stones formed when urine is more alkaline.<sup>[18]</sup> With regard to CaOx stones, a decreased RSR is favorable as it indicates a lower risk of stone formation because of a higher urine output, meaning there is less time for supersaturation to occur. Conversely, an increased RSR suggests an in-

creased risk of stone formation.<sup>[2]</sup> Normally, calcium binds to oxalate introduced from the diet, to lower the levels of oxalate, a known promoter of crystallization within urine. However, the stone forming process is accelerated when urine is more concentrated due to a lower fluid intake, urine output, and a lower level of calcium, but oxalate levels rise.<sup>[2]</sup> Therefore, beverages with a decreased RSR calculation should be recommended for consumption by those most at risk of stones.

### Citrate

High urinary citrate/citric acid excretion reduces the risk of KSD. It is a recognized inhibitor of CaOx as citrate complexes with urinary calcium, which reduces the concentration of calcium available to bind with oxalate and form CaOx stones.<sup>[15]</sup> The protective effects that come with a high level of citrate are preferred for this reason, and coincidentally, many recurrent stone formers commonly present with hypocitraturia.<sup>[5,15]</sup> A significant increase in citric acid excretion was seen with orange, apple, and grapefruit juices,<sup>[19]</sup> as well as blackcurrant juice<sup>[18]</sup> and with an increased intake of water.<sup>[20]</sup> A slight decrease in citric acid excretion was seen with cranberry juice in one study,<sup>[18]</sup> whereas no differences were observed in the case control study with cranberry juice.<sup>[24]</sup> As both studies analyzing orange juice in this review showed the same findings, it confirms the benefits highlighted in previous literature regarding the potassium citrate content making urine less susceptible to crystallization.<sup>[14]</sup> Tackling the common issue of hypocitraturia in kidney stone formers using fluid intake mechanisms as opposed to pharmacological therapies may be something of consideration for future practice.

### Types of water

One of the nine studies in this review specifically compared oligomineral water with bicarbonate-alkaline high-calcium mineral water, which concluded that water with a reduced concentration of calcium should be consumed, as calcium-rich water increases the risk of nephrolithiasis.<sup>[17]</sup> Current literature supports this finding, as in the UK, it has been recommended that drinking bottled water is ideal because of its low calcium levels.<sup>[11]</sup> Distilled, tap, deionized, and Fiuggi waters were used as controls in some of the other studies analyzed in this review. However, as the focus was on the type of juice consumed, these waters acted as a control and lacked further in-depth study.

### Diet control

All studies included in this review followed a standardized diet during the intervention. Literature consistently emphasizes the importance of diet on KSD; hence, it is important to standardize this when assessing the impact of fluid intake.<sup>[5, 11]</sup> Several studies were not included in this review as they failed to do this, thereby making diet a significant confounding factor when analyzing the effect of fluid intake on KSD. Some studies involved

participants keeping a food diary for the duration of the intervention, made of self-selected diet, which was then replicated in each arm of the intervention.<sup>[31,32]</sup> Although this provides some consistency in terms of diet during the studies, it does not eliminate the massive variation in diet between participants, as each individual will have their own dietary preferences when given the choice of choosing their own food to consume. This highlights the necessity of standardizing diet when conducting future studies on fluid intake.

### Benefits, limitations, and areas for future research

This systematic review analyzed a range of fluids and the effects they had on numerous urinary parameters. There is potential for findings from this review to contribute toward preventative therapies for those at risk of KSD. Primary prevention is much more favorable as it is cost-effective, reduces number of hospitalization days, and improves quality of life. Current results from this review may provide a foundation from which certain conclusions can be made with regard to drinks that impact the urinary parameters.

The majority of the studies had small samples. It would be ideal for future studies to have more participants, so that reliable, statistically significant conclusions can be drawn. Some studies involved less than ten participants in some arms, which limits the generalizability of the findings to the wider population. The washout period in cross-over studies is important as it is a period of time given for beverages to be eliminated from the body. In the three cross-over studies, the washout periods between different arms of the study varied, decreasing the validity of such studies. Future cross-over studies should ensure standardized washout periods with minimal variation to allow for more accurate comparisons to be made. An important final point is that all but one study included in this review had no clinical follow-up period. This is an important element to include in future studies as recurrence rates can be calculated, and further analysis can be made on the effect of fluid consumption over time.

### Conclusion

High intake of fluids that are low in calcium seems to reduce the risk of KSD. Certain varieties of fluids, such as grapefruit juice, reduce urine CaOx saturation, with a subsequent reduction in stone formation. Findings from this review could contribute to primary prevention for those at risk of KSD. However, further studies with larger cohorts and clinical follow-up are required, with emphasis on maintaining a standardized diet during the period of study.

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